Friday, 6 February 2004

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 03D-0571

FORMAL COMMENTS ON:

Docket Number : 03D-0571
Comments On : "Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing, and Controls Information; Availability"

Pursuant to a "request for comments" promulgated in ***FEDERAL REGISTER*, 69(4)**, pages 929 – 930, Wednesday, 7 January 2004

Overall, this Draft seems to provide *scientifically sound* and *appropriate* guidance in most areas.

However, this review found a few areas where the Draft needs to be changed so that it adheres to the *applicable* fundamental scientific and regulatory principles of current good manufacturing practice (CGMP) as outlined in 21 CFR Part 210 and 21 CFR PART 211.

The comments being provided to Docket: "**03D-0571**" are based on a review of "**Draft Guidance for Industry on Drug Product, Chemistry, Manufacturing, and Controls Information; Availability** [G:\3969DFT.doc – 1/05/04 – PDF version]."

The comments speak to elements in the Draft that:

- *Though repeatedly mentioned* (e.g., drug substance ***purity***), are not directly addressed in the guidance
- *Though required by sound science*, are not mentioned or discussed (e.g., representative inspection [sampling and evaluation]) or
- Are inadequately (e.g., the level of quality that conforms to CGMP ["Six Sigma"], and the need for explicit release by the firm's quality unit), incorrectly (e.g., process validation), or imprecisely (e.g., methods validation) addressed.

To aid those who will review them, the current "News Gothic MT" font is used and the text is indented on both margins when a rationale or justification is provided.

When a wording change within existing wording is suggested, the comment text is in *italicized News Gothic MT*.

In general, the original text is quoted ("original text") in a "Times New Roman" font and quoted references to CGMP and other FDA-recognized documents are presented in a "Lydian" font.

Should anyone in the Agency who reviews said comments need clarification on a given suggestion or take issue with what has been stated, then they should e-mail (**drking at dr-king.com**) their observation and the scientifically sound rationale that supports their remarks and, where possible, I will provide appropriate clarifying remarks or an answer to their observations.

Respectfully submitted,

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BACKGROUND FOR COMMENTS

The basis for this Draft is set forth in the CGMP regulations – explicitly in **21 CFR Part 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL** and, where applicable, implicitly in **21 CFR Part 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS**.

21 CFR Part 210 begins by stating at **Section 210.**1:

"Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action."

The Federal Food, Drug, and Cosmetic Act (FDC Act) **in 21 U.S.C. 321(g)(1)** states (underlining added):

"The term '*drug*' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). *A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.*"

Thus, a *drug substance* is clearly a *drug*.

Further, **21 CFR 210.2** states:

"Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug and in parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in parts 211 through 226 and parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged."

Based on the preceding and the principles of sound science, many of the requirements explicitly stated in **21 CFR 211** for finished pharmaceuticals clearly apply to the *drug substance*.

A *drug substance* is a *component* in **21 CFR Part 211** and **21 CFR 211.84, "Testing and approval or rejection of components, ...,"** states (*italics* added to emphasize important points):

"(a) *Each lot of components ... shall be withheld from use until* the lot has been *sampled, tested*, or examined, as appropriate, *and released for use by the quality control unit.*

(b) *Representative samples of each shipment of each lot shall be collected for testing ... The number of containers to be sampled*, and the amount of material to be taken from each container, *shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier*, and the quantity needed for analysis and reserve where required by Sec. 211.170.

(c) Samples shall be collected in accordance with the following procedures:
(1) *The containers of components selected shall be cleaned* where necessary, by appropriate means.
(2) *The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, ...*
(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.
(4) *If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.*
(5) *Sample containers shall be identified* so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.
(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) *Samples shall be examined and tested as follows:*
(1) At least one test shall be conducted to verify the identity of each component of a drug product. *Specific identity tests*, if they exist, *shall be used.*
(2) *Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality.* In lieu of such testing by the manufacturer, *a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.*
(3) ...
(4) *When appropriate, components shall be microscopically examined.*
(5) *Each lot of a component ... that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.*
(6) Each lot of a component ... that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) *Any lot of components ... that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use.* Any lot of such material that does not meet such specifications shall be rejected."

Based on the preceding, the critical inspection issues are:

- *All testing* on *each batch* of a *drug substance* must be done on *batch-representative samples*.
- *Given the state of current good manufacturing practice (CGMP) in industry in general is "Six Sigma,"* the inspection (*sampling and testing*) plans must be based on "**statistical criteria for component variability, confidence levels, and degree of precision desired.**"
- The in-process specifications for *each batch* of *drug substance* must also be established using an appropriate valid statistical inspection plan in which representative samples are taken and tested "**to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the**" *drug substance* (21 CFR 211.110(a).
- *Given the current state of analytical science*, the *identity tests* performed on *each batch* must include "**at least one specific identity test.**"
- Unbiased *representative samples* from *each batch* of a *drug substance* that has a defined composition must be tested for conformity with all appropriate written specifications for:
  - *Identity*
  - *"As is" weight-percent purity*,
  - *Strength* (Assay or Potency), and
  - *Quality* (for all *critical* physical and chemical properties other than the explicitly specified *identity*, *purity* and *strength*).
- *Acceptance criteria* for the inspection (*sampling and testing*) conducted by the firm's quality function must assure that the results from the testing of *each batch* of a *drug substance* meet both: a) *each appropriate specification* and b) *appropriate statistical quality control criteria* as a condition for the batch's approval and release. [21 CFR 211.165(d).]

In addition, a few of the definitions in 21 CFR Part 210.3(b) should be noted because they are: a) key to CGMP compliance and b) explicitly or implicitly apply to the *manufacture, processing, packing, packaging, labeling, testing, holding and quality control of a drug substance*.

Those key definitions are:

- "(2) ***Batch*** **means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.**"
- "(3) ***Component*** **means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.**"
- "(4) ***Drug product*** **means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.**"

- "(7) *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."
- "(10) *Lot* means a *batch*, or a *specific identified portion of a batch*, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits."
- "(12) *Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products."
- "(15) *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control."
- "(16) *Strength* means:
  - ***The concentration of the drug substance*** (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or
  - *The potency*, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard)."
- "(17) *Theoretical yield* means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production."
- "(18) *Actual yield* means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product."
- "(19) *Percentage of theoretical yield* means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage."
- "(20) *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units)."
- "(21) *Representative sample* means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled."

With all of the preceding in mind, let us now turn to the text of the guidance.

REVIEW, COMMENTS, AND RATIONALE

1. The text in Lines 33 and 34 states:

"This guidance addresses the information to be submitted for drug substances to ensure continued drug substance and drug product quality (i.e., the identity, strength, quality, purity, and potency)."

That sentence should be revised to read:

"This guidance addresses the information to be submitted for drug substances to ensure *acceptably uniform* drug substance *characteristics* (i.e., the identity, strength, quality, and purity)."

> Unlike the vaporous and convoluted "continued drug substance and drug product quality" used in the Draft and the definition of "quality" as "i.e., …, quality, …," the alternative proposed speaks directly to the critical issue – producing batches of a drug substance that have *acceptably uniform characteristics* in terms of their identity, strength, quality and purity. There is no need to mention the drug product here because: a) the needs of the drug product manufacturing process are addressed in other guidance and b), even though those needs serve to define what is acceptably uniform for a given use, the manufacturing process for the drug product may include drug substance processing steps (e.g., milling or coating) that alter the quality (physiochemical properties) or the strength of the drug substance.
>
> Further, by using the more appropriate term "*characteristics*," the confusing use of the term "quality" is avoided.

2. The text in Lines 79 and 80 states:

"The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required."

That text should be revised to read:

"The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. *Similarly, the use of the word* ***may*** *indicates an optional course or action and the use of the words* ***must*** *or* ***shall*** *indicates an action mandated by specific regulatory or statutory requirements*."

> For completeness, the import of the other key regulatory verbs ("may," must," and "shall") should be explicitly stated.

3. The text in Lines 245 through 252 states:

"• **Characterization (S.3)**: In general, a MF can be referenced for this information. However, the information should be augmented by the applicant, as appropriate. For example, characterization information on physical properties critical to the applicant's product, such as solid state form or particle size distribution, should be included in S.3.1 by the applicant under certain circumstances (e.g., applicant manipulates the physical property (micronizes), the MF holder has not characterized the physical property). Furthermore, information on an applicant's studies to characterize impurities (S.3.2) can be warranted to support the applicant's drug substance controls."

This text should be revised as follows:

"• **Characterization (S.3)**: In general, a *Master File (*MF*)* can be referenced for this information. However, the information should be augmented by the applicant, as appropriate. For example, characterization information on physical properties critical to the applicant's product, such as *solid-state* form or particle size distribution, should be included in S.3.1 by the applicant under certain circumstances (e.g., applicant manipulates the physical property (micronizes), the MF holder has not characterized the physical property). Furthermore, information on an applicant's studies to characterize impurities (S.3.2) can be warranted to support the applicant's drug substance controls. *In all cases, the characterization information must be based on data derived from process representative inspection (sampling and testing) and the use of appropriate statistical procedures that establish the validity of the process-derived specifications for the drug substance at a confidence level that is not less than 95 %.*"

The guidance should make it crystal clear that the drug substance data submitted in support of the characterization of a drug substance must be: a) based on the data from process-representative inspection (sampling and testing) and b) clearly prove the validity of specifications established at a confidence level that is *initially* not less than 95 %.

Moreover, as the manufacturer of the drug substance gains experience, the body of information established should be sufficient to prove the validity of the firm's specifications at a confidence level that is not less than 99 %.

4. The text in Lines 344 and 345 states:

"• Melting or boiling points
• Optical rotation"

For accuracy, that text should be revised to read:

"• Melting *range* or boiling points *at specified pressures*
• Optical *properties (e.g., optical* rotation*, optical rotary dispersion, circular dichromism)*"

5. The text in Lines 409 through 431 states:

"The entire manufacturing process should be depicted (i.e., starting materials through drug substance release testing). See Attachments 1 and 2 for information on starting materials. The flow diagram can be supplemented with information presented in tabular form, if appropriate. The flow diagram should include:

- Each manufacturing step with identification of those steps that are critical. These manufacturing steps can include reaction, workup (e.g., extraction), isolation (e.g., centrifugation, distillation), purification (e.g., chromatography, electrophoresis), processing (e.g., micronization), drug substance release testing.
- The name or code number of the material being processed in each manufacturing step, as appropriate

- Chemical structure (including stereochemical configuration where applicable) or biological identification of starting materials, intermediates, structurally complex reagents, postsynthesis materials, and the drug substance
- Molecular formula and molecular weight of chemical starting materials, intermediates, postsynthesis materials, and drug substance
- Solvents, reagents, and auxiliary materials used in each manufacturing step
- Critical process controls and the points at which they are conducted
- Operating parameters (e.g., temperature, pH, pressure) for each manufacturing step
- An indication of whether intermediates are used in situ or isolated before being used in the next reaction step and which intermediates are considered the final intermediates
- Expected yield (percent) for each reaction step"

For accuracy that text should be revised to read:

"The entire manufacturing process should be depicted (i.e., starting materials through drug substance release *evaluation and drug substance release by the manufacturer's quality unit*). See Attachments 1 and 2 for information on starting materials. The flow diagram can be supplemented with information presented in tabular form, if appropriate. The flow diagram should include:

- Each manufacturing step with identification of those steps that are critical. These manufacturing steps can include reaction, workup (e.g., extraction), isolation (e.g., centrifugation, distillation), purification (e.g., chromatography, electrophoresis), processing (e.g., micronization), drug substance release *evaluation, and all quality release operations (incoming, in-process and final product [finished drug substance])*.
- The name or code number of the material being processed in each manufacturing step, as appropriate**.**
- Chemical structure (including stereochemical configuration where applicable) or biological identification of starting materials, intermediates, structurally complex reagents, postsynthesis materials, and the drug substance**.**
- Molecular formula and molecular weight of chemical starting materials, intermediates, postsynthesis materials, and drug substance**.**
- Solvents, reagents, and auxiliary materials used in each manufacturing step**.**
- Critical process controls, the *point* at which *each process control is* conducted*, and the points at which the firm's quality unit releases a material from one step to the next as well as the final release point***.**
- Operating parameters (e.g., temperature, pH, pressure) for each manufacturing step**.**
- An indication of whether intermediates are used in situ or isolated before being used in the next reaction step and which intermediates are considered the final intermediates**.**
- Expected yield (percent) for each reaction step**.**"

Since some of the suggested specifications are visual (e.g., description) and/or qualitative (e.g., physical shapes observed), the term "testing" should be replaced here by the more appropriate term "*evaluation*."

Just as the CGMP regulations for drugs states, "**Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products**" (21 CFR 210.3(b)(12), the CGMP expectation for drug substances must have parallel expectations. Thus, the flow diagrams need to include the points at which the manufacturer's quality unit releases a material to the next step. The general points are: a) the release of an incoming "raw" material for use in the process, b) any release of an in-process material from one step to the next and c) release of the finished drug substance into commerce. These should be explicitly included in the process flow diagrams provided.

6. The text in Lines 708 through 715 states:

"The following information should be included in the application to support the proposed starting materials:

- A list of proposed starting materials and/or information on plant or animal starting materials
- A flow diagram
- A specification for each starting material
- Justification for the proposed starting materials, when appropriate"

This text should be revised to follow the same indented alphabetic header format as that used in the section that follows, "2. Reagents, Solvents and Materials." With the preceding in mind, this reviewer would suggest that the text be revised as follows:

"*a. List of Proposed Starting Materials And/Or Information on Plant or Animal Materials*

A detailed list of the proposed starting materials and/or information on any plant- or animal- based materials used in the manufacture of a drug substance should be provided.

b. Flow Diagram

Where appropriate, a flow diagram outlining the conversion of purchased incoming materials into the starting materials should be provided. In addition, a flow diagram should be provided showing the controls imposed on any plant- or animal- based materials used by the process to ensure that their use does not introduce any adventitious viral or prionic (e.g., transmissible spongiform encephalopathy [TSE]) agent that may survive the process.

c. A Specification For Each Starting Material And/Or Plant- Or Animal- Based Material

A scientifically sound, appropriate specification should be provided for each material. Both attribute and variable specifications should be statistics based limits or ranges derived from the results obtained from population-representative samples and should include the population percentage covered by the specification and its confidence level. The specification sheet for each material listed should list all tests to which the material will conform and the associated acceptance criteria. The physical properties that may affect the critical characteristics of the drug substance should be included in the material's specifications. It should also include a reference to the analytical procedures that will be used to perform each test. At a minimum, the reference should identify the specific type of analytical procedure used (e.g., potentiometric titration, KBr-pellet infrared transmission spectrographic scan, packed-column GC-FID analysis, capillary-column GC-ECD analysis, packed-column HPLC-UV analysis).

The scientifically sound tests and acceptance criteria in each specification should be appropriate for the kind of material and its intended use. These should also be consistent with the quality of the material used to manufacture the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E). The appropriate "as is" purity of each should be determined for each discrete material.

d. Justification For The Materials Proposed

Unless the reason for the use of a given material is obvious, the manufacturer should include an appropriately detailed justification for the use of each material in the production process."

The text used here should be more detailed and parallel the text layout used for section "*2. Reagents, Systems, and Auxiliary Materials*." In addition, the text should explicitly state that the approach used should be derived from the *scientifically sound* and *appropriate statistics-based inspection* (sampling and evaluation) of *population-representative samples*.

7. The text in Lines 459 through 461 states:

"• Type of analytical procedure (e.g., HPLC) used for each process test

• Identification of intermediates, postsynthesis materials, and unfinished drug substance that are tested (details should be provided in S.2.4)"

That text should be revised to read:

"• Type of analytical procedure (e.g., *Description, pH, LOD, and* HPLC-*UV*) used for each process *evaluation*"

• Identification of intermediates, postsynthesis materials, and unfinished drug substance that are *evaluated* (details should be provided in S.2.4)"

Because some of the analytical procedures used are examinations and not quantitative or limit tests, the terms "*evaluation*" and "*evaluated*" are more appropriate here than the Draft's use of the terms "test" and "tested."

8. The text in Lines 505 through 517 states:

"The term includes:

- Operating parameters — conditions that can be adjusted to control the manufacturing process (e.g., temperature, pH, time, mixing speed)
- Environmental controls — conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)
- Process tests — measures used to monitor and assess the performance of an on-going manufacturing operation (e.g., analysis to determine concentration of reactant or product, measuring hydrogen gas uptake during hydrogenation)
- In-process material tests — measures used to assess the quality attributes and/or the suitability for use in the manufacturing process of an isolated intermediate, postsynthesis material, or unfinished drug substance"

That text should be revised to read:

"The term includes:

- Operating parameters — conditions that can be adjusted to control the manufacturing process (e.g., temperature, pH, time, mixing speed)
- Environmental controls — conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)
- Process tests — measures used to monitor and assess the performance of an on-going manufacturing operation (e.g., analysis to determine concentration of reactant or product, measuring hydrogen gas uptake during hydrogenation)
- *Process examinations — visual checks used to describe qualitative aspects (e.g., Description, Color, Clarity) of a process solution, mixture or material*
- In-process material *evaluations* — measures *and examinations* used to assess the quality *characteristics* and/or the suitability for use in the manufacturing process of an isolated intermediate, postsynthesis material, or unfinished drug substance"

For accuracy, the list needs to include examinations in addition to tests. When both are being addressed, the term "*evaluations*" should be used in place of the Draft's "tests."

9. The text in Lines 505 through 517 states:

"Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. Process tests and in-process material tests can be performed on-line, at-line, or off-line. All process controls, critical or otherwise, should be included in the description of the manufacturing process."

That text should be revised to read:

"Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. Process *evaluations (tests and examinations [including classifications])* and in-process material *evaluations* can be performed on-line, at-line, or off-line. All process controls, critical or otherwise, should be included in the description of the manufacturing process."

> Again, the term "*evaluations*" is more appropriate than the Draft's "tests." This is the case because the term "*evaluations*" encompasses: a) the classification of materials as acceptable, not acceptable or indeterminate, b) examinations that describe the appearance of materials, and c) tests that qualitatively (e.g., an indicator test for the presence of magnesium), semi-quantitatively (e.g., a limit test for lead), or quantitatively (e.g., an assay for the level of chloride in sodium chloride) measure the level of some variable in a material.

10. The text in Lines 538 through 543 states:

"All of the operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified as critical in the flow diagram and description of the manufacturing process in this section of the application (S.2.2) and in S.2.4. All tests on intermediates, postsynthesis materials, and unfinished drug substance should be listed in the description of the manufacturing process in S.2.2 and described in S.2.4."

That text should be revised to read:

"All of the operating parameters, environmental conditions, and process *evaluations* that ensure each critical manufacturing step is properly controlled should be specifically identified as critical in the flow diagram and description of the manufacturing process in this section of the application (S.2.2) and in S.2.4. All *evaluations* on intermediates, postsynthesis materials, and unfinished drug substance should be listed in the description of the manufacturing process in S.2.2 and described in S.2.4."

> Again, the use of the term "*evaluations*" is more appropriate here than the Draft's "tests." This is especially true when the manufacturer uses analysis systems that classify materials rather than directly assessing the value of one or more variable factors.

11. Figure 1:

The term "**Tests**" as used in **Figure 1** (page 15) should be replaced with the term "***Evaluations***."

> See the preceding rationales that support using the term "***Evaluation***s" in place of the Draft's use of the term "**Tests**."

12. The text in Lines 574 through 576 states:

"Continuation of a manufacturing step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing."

That text should be revised to read:

"Continuation of a manufacturing step after a process *evaluation* has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing."

> See the preceding rationales that support using the term "*evaluation*" in place of the Draft's use of the term "test."

13. The text in Lines 649 through 652 states:

"Controls on regenerated material can include, for example, a maximum number of times the material will be regenerated and/or tests to determine the continued suitability (e.g., column efficiency) of the material."

That text should be revised to read:

"Controls on regenerated material can include, for example, a maximum number of times the material will be regenerated and/or *the evaluations used* to determine the continued suitability (e.g., column efficiency) of the material."

> See the preceding rationales that support using the term "*evaluations*" in place of the Draft's use of the term "tests." In addition, to improve the clarity of the text, the wording around the term "*evaluations*" has been revised as shown.

14. The text in Lines 738 through 753 states:

"b. Specification

A specification should be provided for each material. The specification sheet should list all tests to which the material will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. At a minimum, the reference should identify the type of analytical procedure used (e.g., GC, HPLC).

The tests and acceptance criteria in each specification should be appropriate for the kind of material and its intended use, and should be consistent with the quality of the material used to manufacture the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E). For example, extensive purity testing of an inorganic base used to adjust pH would

not normally be warranted, but testing of enantiomeric purity might be appropriate for an optically active organic acid used in a resolution step.

Water used in the manufacture of drug substances should be of appropriate quality for its intended use."

The preceding text should be changed to read:

"b. Specification

A *scientifically sound, appropriate* specification should be provided for each material. *Both attribute and variable specifications should be statistics based limits or ranges derived from the results obtained from population-representative samples and should include the population percentage covered by the specification and its confidence level.* The specification sheet *for each material* should list all *evaluations* to which the material will conform and the associated acceptance criteria. *The physical properties that may affect the critical characteristics of the drug substance should be included in the material's specifications. It* should also include a reference to the analytical procedures that will be used to perform each *evaluation*. At a minimum, the reference should identify the *specific* type of analytical procedure used (e.g., *potentiometric titration, KBr-pellet infrared transmission spectrographic scan, packed-column GC-TCD analysis, packed-column HPLC-UV analysis*).

The *scientifically sound evaluations* and acceptance criteria in each specification should be appropriate for the kind of material and its intended use. *These* should *also* be consistent with the quality of the material used to manufacture the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E). For example, extensive purity testing of an inorganic base used to adjust pH would not normally be warranted, but testing of enantiomeric purity might be appropriate for an optically active organic acid used in a resolution step. *However, the appropriate "as is" purity should be determined for each discrete material.*

*The w*ater used in *any aspect of the process for* the manufacture of drug substances, *including equipment cleaning*, should be of appropriate quality for its intended use.

c. Justification

Unless the reason for the use of a given material is obvious, the manufacturer should include an appropriately detailed justification for the use of each material in the production process."

> The text used here should be more detailed. In addition, the text should explicitly state that the approach used should be derived from the *scientifically sound* and *appropriate statistics-based inspection* (*sampling* and *evaluation*) of *population-representative samples*. The term "*evaluation*" should be used in place of the Draft's "test." This is especially true when the manufacturer uses analysis systems that classify materials rather than directly assessing the value of one or more variable factors. Finally, as was the case for starting materials, the manufacturer should provide a justification section for the materials chosen.

15. The text in Lines 769 through 780 states:

"In this section of the application, all critical operating parameters, environmental controls, process tests and all tests performed on intermediates, postsynthesis materials, and unfinished drug substance should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified. Any of the tests and associated numeric ranges, limits, or acceptance criteria for intermediates, postsynthesis materials, or unfinished drug substance that are judged to be non-critical can be indicated as such. FDA recommends that the noncritical be listed separately from the critical tests to distinguish them from the critical tests that constitute the specification for the intermediate, postsynthesis material, or unfinished drug substance.

For all critical process controls, the associated numeric ranges, limits, or acceptance criteria should be justified and a brief description of the test provided."

That text should be revised to read:

"In this section of the application, all critical operating parameters, environmental controls, process *evaluations* and all *evaluations* performed on intermediates, postsynthesis materials, and unfinished drug substance should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified. Any of the *evaluations* and associated numeric ranges, limits, or acceptance criteria for intermediates, postsynthesis materials, or unfinished drug substance that are judged to be non-critical can be indicated as such. FDA recommends that the noncritical be listed separately from the critical *evaluations* to distinguish them from the critical *evaluations* that constitute the specification for the intermediate, postsynthesis material, or unfinished drug substance.

For all critical process controls, the associated numeric ranges, limits, or acceptance criteria should be justified and a brief description of the *evaluation procedure* provided."

> Because the process controls can include examination and classification procedures in addition to procedures that measure a variable's level, the more appropriate term to use is "*evaluation*."

16. The text in Lines 795 through 812 states:

"• **Tests Used In Lieu of Drug Substance Tests**

In some cases, results from tests performed during the manufacturing process (e.g., process tests, tests on intermediates, postsynthesis materials, or unfinished drug substance) can be used in lieu of testing the drug substance to satisfy a test listed in the drug substance specification. For example, testing to determine the level of a residual solvent on an isolated intermediate may be sufficient to satisfy a test listed in the drug substance specification provided in S.4.1. This approach, however, should be supported with data that demonstrate that test results or drug substance performance characteristics do not undergo an adverse change from the in-process stage to drug substance. These data, along with the analytical procedure and associated validation information, should be provided in S.2.4. Information should be included in the method validation package (R.3.S), as appropriate. When the same analytical procedure is used for both the in-process test and the drug substance test, the acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the drug substance specification. Tests performed in-process in lieu of testing the drug substance should be included in the drug substance specification (S.4.1) and the results of such tests should be included in the batch analysis report (e.g., certificate of analysis)."

The preceding text should be changed to read:

"• ***Evaluations* Used In Lieu of Drug Substance *Evaluations***

"In some cases, *provided the evaluations are performed on batch-representative samples, the* results from *evaluations* performed during the manufacturing process (e.g., process *evaluations*, *evaluations* on intermediates, postsynthesis materials, or unfinished drug substance) *may* be used *when the results obtained have been proven to be the same as those for the drug substance* in lieu of *evaluating* the drug substance to satisfy *an evaluation* listed in the drug substance specification. For example, testing to determine the level of a residual solvent on an isolated intermediate may be sufficient to satisfy a test listed in the drug substance specification provided in S.4.1. This approach, however, should be supported with data that demonstrate that *evaluation* results or drug substance performance characteristics do not undergo an adverse change from the in-process stage to drug substance. These data, along with the analytical procedure and associated validation information, should be provided in S.2.4. Information should be included in the method validation package (R.3.S), as appropriate. When the same analytical procedure is used for both the in-process *evaluation* and the drug substance *evaluation*, the acceptance criterion *or criteria* for the in-process *evaluation* should be identical to or tighter than the *corresponding* acceptance criterion *or criteria* in the drug substance specification. *Evaluations* performed in-process in lieu of *evaluating* the drug substance should be included in the drug substance specification (S.4.1) and the results of such *evaluations* should be included in the batch analysis report (e.g., certificate of analysis)"

The scientific issues of *representative* results and test result equivalence between the drug substance and an earlier material need to be explicitly addressed. In general, the more general terms "*evaluation*," "*evaluations*" and "*evaluating*" should be used in place of the Draft's terms "test," "tests" and testing." Finally, a given analytical procedure may generate results that require more than one acceptance criterion (e.g., an HPLC-UV procedure for organic impurities).

17. The text in Line 828 states:

"• The proposed specification for the intermediate"

That text should be changed to read:

"• The proposed specification for the intermediate *that, at a minimum, includes scientifically sound and appropriate: a) specific identity requirements, b) "as is" weight- or volume- % purity and c) limits on the key impurities permitted*"

The guidance should include these specifications to set a minimum Agency expectation that recognizes that "Identification," "Assay," and "Total organic impurity" are NOT the fundamental characteristics required to specify the key variable properties of an intermediate.

18. The text in Lines 868 through 888 states:

"**E. Process Validation and/or Evaluation (S.2.5)**

Validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug substance, packaging components) should be submitted in this section of the application for sterile

drug substances. Furthermore, if a step in the manufacturing process is designed to reduce the amount of microbial contamination, such as for certain drug substances derived from biological sources, information to support the appropriateness of the step should be included. Submission of other manufacturing process validation information in the application is not necessary for most drug substances.[15] However, for naturally derived protein drug substances, information concerning the evaluation of purification processes related to the removal of impurities should be provided in this section. When applicable, validation information should be provided for processes used to control adventitious agents. This information should be included in A.2.

Submission of validation information for reprocessing and reworking operations usually is not warranted. However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances)."

[15] All manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits.

The preceding text should be changed to read:

"**E. *Initial* Process Validation and/or Evaluation (S.2.5)**

*The manufacturer's initial process v*alidation information relating to the adequacy and efficacy of any sterilization process (e.g., drug substance, packaging components) should be submitted in this section of the application for sterile drug substances. Furthermore, if a step in the manufacturing process is designed to reduce the amount of microbial contamination, such as for certain drug substances derived from biological sources, information to support the appropriateness of the step should be included. Submission of other manufacturing process *initial* validation information in the application *may* not *be* necessary for most drug substances.[15] However, for naturally derived protein drug substances, information concerning the *initial* evaluation of purification processes related to the removal of impurities should be provided in this section. When applicable, *initial* validation information should be provided for processes used to control adventitious agents. In all cases, the information provided should include the rationale that establishes the validity of the approaches and controls used to validate the process or any aspect thereof. This information should be included in A.2.

Submission of *initial* validation information for reprocessing and reworking operations *may* not *be* warranted. However, it *is* warranted when the reprocessing or reworking operation is of the type for which *initial* process validation information *should be* submitted when routinely performed or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances)."

[15] *The validity of a*ll manufacturing processes should be *proven during process development and the manufacture of each commercial-scale batch should serve to validate the process established. In* most cases, *much of the raw data that supports the initial* validation *should be* reviewed during facility audits. *However, the data that justifies the validity of the process should be included in the submission along with the firm's supporting rationale for the validity of the process.*

The validation of any process is a lifelong ongoing journey and not, as the Draft portrays it, a destination. The Agency needs to recognize this reality

and stop trying to misrepresent reality. The applicable "in-process" CGMP regulations set forth explicitly in the regulations for drug products (finished pharmaceuticals) at **21 CFR 211.110(a)**, "**To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**" (underlining emphasis added), clearly establish that validation is an each batch journey. In today's terms, validation is a set of qualification activities that span the life of the process. One self-consistent "validation" set of qualifications is the set: "Design Qualification (DQ), Build Qualification (BQ), Operation Qualification (OQ), Evaluation Qualification (EQ), Maintenance Qualification (MQ), and Closure Qualification (CQ)" that replaces the less consistent incomplete set: "Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ)." The incomplete set leaves out the fact that the process must be designed and constructed (built); a process cannot simply be installed. Moreover, the incomplete set stops with PQ even though validation is clearly an ongoing each batch process. Thus, the text needs to be changed to conform to the preceding scientific and regulatory realities – validation is a lifelong activity.

19. The text in Lines 1105 through 1126 states:

"The specification sheet should list all tests to which each batch of a drug substance will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data the analytical procedure should be described in S.7.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VI.E). The specification from the applicant and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacturer's certificate of analysis (COA).[18] Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- Tests that can be performed in-process (e.g., Process tests, intermediate tests, postsynthesis material tests, unfinished drug substance tests) in lieu of testing the drug substance (the results of such tests should be included in the batch analysis report (e.g., Certificate of analysis))
- All analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[19]
- Acceptance criteria for the test using the regulatory analytical procedure and acceptance criteria for any alternative analytical procedures
- Release and shelf-life acceptance criteria when both are used

[18] The applicant and/or drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)). The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate the tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices.

[19] Certain *General Chapters* in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the *European Pharmacopoeia* (EP) and the *Japanese Pharmacopoeia* (JP). However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive."

The preceding text should be changed to read:

"The specification sheet should list all *evaluations* to which each batch of a drug substance will conform and the associated acceptance criteria, and should also include a reference to the analytical procedures that will be used to perform each *evaluation*. Acceptance criteria are numerical limits, ranges, or other criteria for the *evaluations* described. *These should be based on the application of appropriate statistical procedures that have been proven to appropriately predict batch and process limits based on the data derived from the evaluation of an appropriate number of lot or batch representative samples from a sufficient number of developmental and preproduction lots.* If an analytical procedure will be used only to generate stability data the analytical procedure should be described in S.7.3. Justified interim acceptance criteria and *evaluation procedures* with sunset provisions should be included in the specification (see section VI.E). The specification from the applicant and/or drug product manufacturer should identify the *evaluation procedures* that it *and/or they* will routinely perform and the *evaluation* results that will be accepted from the drug substance manufacturer's certificate of analysis (COA).[18] Presentation of information in a tabular format is suggested. The specification sheet should also identify:

- *Evaluations* that can be performed in-process (e.g., *p*rocess *evaluations*, intermediate *evaluations*, postsynthesis material *evaluations*, unfinished drug substance *evaluations*) in lieu of *evaluating* the drug substance (the results of such *evaluations* should be included in the batch analysis report (e.g., *c*ertificate of analysis *or report of analysis*)
- All analytical procedures that will be used for *an evaluation*; identifying which are*: a) the firm's established batch release procedures,*[18A] *b) post-release "in commerce"* regulatory *procedures when such exist, c) the firm's established stability-indicating methods,*[18B] and *d)* alternative analytical procedures when multiple analytical procedures *are required or specified* for *a given evaluation*[19]
- *Scientifically sound and appropriate a*cceptance criteria for *each of the firms' required or specified* analytical procedures
- Release and shelf-life acceptance criteria when both are *required or specified*

[18] *Provided the firms commit to performing at least one specific identity test, t*he applicant and/or drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's results at appropriate intervals (21 CFR 211.84(d)(2)). The reliability of the analyses need not be established at the time the application is submitted. *However, firms should establish the reliability of the supplier's results whenever the supplier has not been previously used by the manufacturer and/or the applicant. Moreover,* the specification should indicate the *evaluations, including at least one specific identity test,* which will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices.

18A *The firm must have and submit scientifically sound batch release procedures and acceptance criteria. These must be based on the results derived from the evaluation of representative samples for a sufficient number of developmental or pre-production batches. Because only a small number of samples are evaluated, the batch acceptance established must be appropriately inside of the lifetime criteria established for the drug substance in an official compendium or the corresponding values established by the manufacturer for non-compendial drug substances. As specified in 21 CFR 211.165(d) for the drug product, the drug substance acceptance criteria must* "**be adequate to assure that**" *each batch of the drug substance meets* "**each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release.**"

18B *Even when the drug substance is stable with no evidence of degradation when stored at the highest temperature permitted for more than the maximum time established by the manufacturer of the drug substance, the firm must have and submit scientifically sound stability indicating methods that have been proven to be capable of adequately measuring and tracking the degradation of the drug substance.*

19 Certain *General Chapters* in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the *European Pharmacopoeia* (EP) and the *Japanese Pharmacopoeia* (JP). However, where a difference appears, or in the event of dispute, the results obtained from the USP procedure *are* conclusive.

In most cases, the more general terms "*evaluation*," "*evaluations*," or "*evaluation procedures*" should be used in place of the Draft's terms "test" or "tests." The guidance needs to explicitly state that the firms' acceptance criteria must be founded on the scientifically sound treatment of lot or batch representative data from a sufficient number of developmental or pre-production lots or batches.

In addition, the guidance needs to make it clear that the firms must have drug-substance release criteria and that these must be appropriately inside of the firms' or, when they exist, the compendial post-release criteria for the drug substance.

Similarly, the need for stability indicating analytical procedures and acceptance criteria needs to be stated.

20. To conform to CGMP expectations for identity and purity as well as to better reflect key physical properties of a drug substance, Table 1 following Line 1129 should be changed as follows:

Table 1: Specification for Synthesized Drug Substance X			
Evaluations	*Batch-Release* Acceptance Criteria *[Post-Release Acceptance Criteria]*	*Batch-Release* Analytical Procedure *[Post-release (Compendial or The "In Commerce") Analytical Procedure]*	Alternative Analytical Procedure
Appearance	White crystalline powder *[White to off-white crystalline powder]*	Visual *comparison to "Milk" White reference standard, AP*[1] *# XYZ* *[Visual]*	None AP # XYZ
Specific Identity Test	*Batch-release Analytical Procedure: The "as is" 0.5-%-KBr-Pellet high-resolution FT-IR spectrum (1000-scan average) of a container-**representative** subsample from each container matches in both scaled amplitude to within 5 % relative and location to within 0.5 cm^{-1} a stored 0.5%-KBr-Pellet high-resolution FT-IR spectrum for the firm's primary reference standard material for all components having a signal-to-noise ratio that is greater than five (5). [Same]*	*FT-IR, AP # DEF* *[Same]*	*None*
Identification Tests	*Batch-Release* Analytical Procedure: (1) Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the assay. *[Same]* (2) Spectra is similar to that of corresponding preparation of the reference standard *[Same]* (3) Responds to the tests for sulfate *[Same]* Alternative Analytical Procedure: Conforms to established spectral library	(All performed *for Release [(1) & (3) performed Post-Release]*) (1) HPLC, AP # EFG *[Same]* (2) Infrared Absorption, USP <197M> *[Same]* (3) Sulfate, USP <191> *[Same]*	Near Infrared Analysis[2], AP # ABC
Melting Range	*101°C* to 102°C *[100°C to 101.7°C]*	AP #BCD *[Same]*	USP <741>, Class Ib
Residue on Ignition	NMT[3] *0.09% with an RSD ("n" NLT 5) of NMT 3% [NMT* 0.1%*]*	USP <281>, ignition temp. 225°C *[Same]*	*None*
Heavy Metals	*LT* 0.0009% *[NMT* 0.001%*]*	USP <231>, Method II *[Same]*	*None*
Loss on Drying	NMT *0.75% with an RSD ("n" NLT 5) [NMT* 1.0%*]*	USP <731>, dry at 45°C to a constant weight *[Same]*	*None*
Assay	NLT[4] 99% and NMT 101% of $C_xH_xN_xO_x$, calculated on the dried basis, *with an RSD ("n" NLT 5) of NMT 1 % [NLT* 98.0% *and NMT*102.0% *on the same basis]*	HPLC, AP # EFG *[Same]*	*None*

Table 1: Specification for Synthesized Drug Substance X			
Evaluations	*Batch-Release* Acceptance Criteria *[Post-Release Acceptance Criteria]*	*Batch-Release* Analytical Procedure *[Post-release (Compendial or The "In Commerce") Analytical Procedure]*	Alternative Analytical Procedure
"As is" Weight-% Purity	*NLT 98.5% and NMT 99.3 % with an RSD ("n" NLT 5) of NMT 5% for the impurities used to compute the sum [NLT 97.5% and NMT 99.5%]*	*100 % – Σ Impurities, AP # FGH [Same]*	*None*
Organic Impurities Specified Impurities • Impurity A • Impurity B • Impurity at RRT[5] XX Unspecified Impurities • Any Unspecified Total Organic Impurities	 NMT *0.1 % with an RSD ("n" NLT 5) of NMT 3 % [NMT* 0.3%*]* NMT *0.25% with an RSD ("n" NLT 5) of NMT 2% [NMT* 0.4%*]* NMT *0.17% with an RSD ("n" NLT 5) of NMT 2 % [NMT* 0.3%*]* NMT *0.05% with an RSD ("n" NLT 5) of NMT 3 % [NMT* 0.1%*]* NMT *0.6% with an RSD ("n" NLT 5) of NMT 2.5% [NMT* 1.0%*]*	HPLC; AP # EFG *[Same]*	*None*
Residual Solvent A	NMT 200 ppm in Drug Substance X or NMT 200 ppm in Intermediate C	GC, AP # XYZ *[Same]*	*None*
Density *Bulk Density (BD)* *Tapped Density (TD)*	 *0.57 to 0.62 g/cm³ with an RSD ("n" NLT 3) of NMT 3 % [0.53 to 0.66 g/cm³]* *0.75 to 0.79 g/cm³ with an RSD ("n" NLT 3) of NMT 2 % [0.7 to 0.81 g/cm³]*	*AP # GHI [Same]*	*None*
Flow Index (FI = BD/TD)	*NLT 0.72 with an RSD ("n" NLT 3) of NMT 2.5 % [NLT 0.65]*	*AP # GHI [Same]*	*None*
Particle Size Distribution (D) • D (10%) • D (50%) • D (90%) • *D (100 %)*	 NMT *4.5* microns *[NMT* 5 *microns]* NMT *9* microns *[NMT* 10 *microns]* NMT *25* microns *[NMT* 30 *microns]* *NMT 45 microns [NMT 60 microns]*	Brand X Particle Size Analyzer *operating in the "Particle in Air" Mode,* AP # LMN *[Same]*	*None*

[1] AP = Analytical Procedure
[2] Test will be performed on-line during final drying operation.
[3] NMT = not more than
[4] NLT = not less than
[5] RRT = relative retention time

Though the clear CGMP requirements expressly include "identity" and "purity," the Draft does NOT include evaluation procedures or acceptance criteria for these items. Instead of an identity test, the Draft proposes some "Identification Tests."

The problem with "Identification Tests" are that they do not identify the drug substance to the exclusion of all other drug substances and/or all other related physical forms of the drug substance. For example, while the failure of the retention times to match clearly can be used to assert that the substances are different, retention-time match cannot validly be used to assert that the material being tested is the same as the desired drug substance. Likewise, the similarity of a single "prepared" test sample to a "prepared" reference material does not establish the identity of the batch of material being tested to that of the firm's primary standard (submitted batches or lots upon which the firm's FDA acceptance rests). Finally, it should be obvious that a qualitative test for sulfate only identifies the presence of sulfate; it does not identify the material being tested. Based on all of the above, a specific identify test on a set of representative samples that span the batch or lot, such as the one proposed, or multiple tests on similarly representative samples must be included in the specification for a drug substance.

Again, instead of including a CGMP-compliant "as is" weight-percent ***purity***, the Draft only proposes an "Assay." The drug-product CGMP regulations require the manufacturer of the drug product to determine the "as is" purity of the drug substance in order to properly formulate each batch of drug product. Repeatedly, this Draft also speaks of the need to determine drug substance purity, but does not provide for or address it in the guidance provided. The proposed revision addresses this obvious deficiency. Though not stated, the "impurity" assessments used to determine the total impurity must be performed on samples that are representative of each batch or lot tested. Moreover, unlike those who would claim that the proposed "Assay" is an adequate substitute for purity, this reviewer knows that an "Assay" test is not a valid measure of material purity. Moreover, the number of representative "as is" Assay tests needed to define the "purity" (on the order of 50 to 500 tests depending upon the overall uncertainties in the testing performed) is much larger than the number of determinations needed for a valid purity by difference determination. In addition, the RSD values for "n" batch *representative* samples are included as minimum statistical quality control criteria that must be included in the release criteria for a batch of drug substance. [**Note:** *Unlike the USP monographs and evaluations that are properly "any grab sample" based*, the release samples must be of sufficient size to be batch representative.] Hopefully, if the Agency truly supports science-based guidance, this Draft will be corrected as indicated.

In addition, the critical physical material handling specifications extend beyond the distribution of the sizes of the particles in a batch. At a minimum, the density and flow properties of each batch of drug substance need to be specified so that the formulator will have some idea of how much material can be loaded into the blender, how easily it can be blended and with which ingredients it can be easily blended. Moreover, each batch's or lot's particle-size specifications should be determined using a suitable "particle in air" test system and should include an upper limit.

This reviewer has therefore included specification items to address each of the preceding issues including statistical quality control criteria.

21. Again, to conform to CGMP expectations for identity and purity as well as to better reflect key physical properties of a drug substance, Table 2 following Line 1131 should be changed as follows:

Table 2: Specification for a Highly Purified Naturally Derived Protein Drug Substance Y[1]		
Evaluations	Acceptance Criteria *For Batch Release* *[Post-release Acceptance Criteria]*	*Batch Release* Analytical Procedure (AP)[2] *[Post-Release (Compendial) Procedure]*
Appearance	White lyophilized powder *[White to slightly off-white powder]*	Visual *[Same]*
Specific Identity Test	*Batch Acceptance Analytical Procedure: The "as is" 0.7-%-KBr-Pellet high-resolution FT-IR spectrum (10,000-scan average) of a container-**representative** subsample from each container matches in both scaled amplitude to within 5 % relative and location to within 1 cm $^{-1}$ a stored 0.7%-KBr-Pellet high-resolution FT-IR spectrum for the firm's primary reference standard material for all components having a signal-to-noise ratio that is greater than five (5). [Same]*	*(Performed on Each Container)* *FT-IR, AP # O123 [Same]*
Identification Tests:		
Identification Test #1	Retention time of the major peak corresponds to that of the reference standard *[Same]*	RP-HPLC[3], AP # A123 *[Same]*
Identification Test #2	Retention time of the major peak corresponds to that of the reference standard *[Same]*	SE-HPLC[4], AP # B345 *[Same]*
Identification Test #3	Major bands of sample correspond to major bands of the reference standard and account for NLT[5] *88%* of total signal *[Same procedure with NLT 85 % of the total signal]*	Isoform pattern by isoelectric focusing/ Coomassie Blue staining and scanning, AP # C678 *[Same]*
Assays:		
Monomer	NLT *97%* with *an RSD ("n" NLT 7) of NMT 2 % [NLT 95%]*	SE-HPLC, AP # B345 [Same]
Specific Biological Activity	*NLT 30,000* International Units (IU)/mg *with an RSD ("n" NLT 7) of NMT 5 %* *[20,000-30,000 IU/mg]*	Mouse Bioassay, AP # D901 and Lowry, AP# D902 *[Same]*
Purity Tests:		
Dimers and aggregates	NMT[6] *1% with an RSD ("n" NLT 7) of NMT 4 %* *[NMT 2%]*	SE-HPLC, AP # B345 *[Same]*
Oxidized Forms	Area of the peaks corresponding to oxidized forms is NMT *1.5%* of the sum of peak areas of intact and oxidized products *with an RSD ("n" NLT 7) of NMT 5 %* *[Same evaluation with a "NMT 3%" limit]*	RP-HPLC, AP # E234 *[Same]*
Electrophoretic purity	No additional significant band (NMT *1.5%*) when compared to the profile of the reference *[Same evaluation with a "NMT 2 %" limit]*	SDS-PAGE[7] dissociated and non-dissociated/silver stain, AP # F567 *[Same]*
Bacterial endotoxins	NMT *60* Endotoxin Units (EU)/mg *[NMT 100 EU/mg]*	USP <85>, Gel-Clot Techniques *[Same]*
Microbial Limits	NMT *60* Colony Forming Units (CFU)/*100* mg &	USP <61>, Plate Method

Table 2: Specification for a Highly Purified Naturally Derived Protein Drug Substance Y[1]		
Evaluations	Acceptance Criteria *For Batch Release [Post-release Acceptance Criteria]*	*Batch Release* Analytical Procedure (AP)[2] *[Post-Release (Compendial) Procedure]*
	Absence of specified indicator organisms *[NMT 10 CFU/10 mg & Absence of specified indicator organisms]]*	*[Same]*
Water Content	NMT *4%* (w/w) *with an RSD ("n" NLT 7) of NMT 1.5% [NMT 5% (w/w)]*	USP <921>, Method Ia *[Same]*
"As is" Weight-% Purity	*NLT 85.0 and NMT 90.5 % with an RSD ("n" NLT 7) of NMT 5 % for the impurities total [NLT 83.0 %]*	*100 % – Σ Impurities, AP # G678 [Same]*
pH	*7.2 – 7.7 in a solution prepared using pH 6.8 to 7.2 water and* 10 mg of Drug Substance Y/mL *[7.0 – 8.0 under the same test conditions as for Release]*	USP<791> *[Same]*
Density		*AP # H789 [Same]*
Bulk Density (BD) *Tapped Density (TD)*	*0.45 to 0.51 g/cm³ with an RSD ("n" NLT 3) of NMT 4 % [0.43 to 0.54]* *0.63 to 0.72 g/cm³ with an RSD ("n" NLT 3) of NMT 4 % [0.61 to 0.74*	
Flow Index (FI = BD/TD)	*NLT 0.62 with an RSD ("n" NLT 3) of NMT 4% [NLT 0.60]*	*AP # H789 [Same]*
Particle Size Distribution (D)		Brand X Particle Size Analyzer *operating in the "Particle in Air" Mode, AP # I890 [Same]*
• *D (10%)* • *D (50%)* • *D (90%)* • *D (100 %)*	*NMT 50 microns [NMT 55 microns]* *NMT 120 microns [NMT 125 microns]* *NMT 150 microns [NMT 180 microns]* *NMT 250 microns [NMT 325 microns]*	

[1]This is an example specification and is not intended to imply that these are the typical tests and acceptance criteria for a naturally derived protein drug substance. The tests and acceptance criteria appropriate for a particular naturally derived protein drug substance depend on the biological source, manufacturing process, and its intended use. For example, (1) residual monoclonal antibody (mAbs) should be monitored for drug substances purified by affinity chromatography using mAbs; (2) for proteins that are not as highly purified, less vigorous acceptance criteria for purity tests may be appropriate; and (3) the need for bacterial endotoxins and microbial limits testing and the associated acceptance criteria depend on the route of administration of the drug product and the controls used during the manufacture of the drug product.

[2]There are no alternative analytical procedures specified for Drug Substance Y

[3]RP-HPLC = reverse phase high-pressure liquid chromatography

[4]SE-HPLC = size exclusion high-pressure liquid chromatography

[5] NLT = not less than

[6] NMT = not more than

[7]SDS-PAGE = Sodium dodecyl sulfate polyacrylamide gel electorphoresis

Though the clear CGMP requirements expressly include "identity" and "purity," the Draft does NOT include tests for these items. Similarly, the physical material properties of all drug substances need to be specified. In general, the rationales for the proposed changes to the "**Table 2**" example are the same as those presented for the "**Table 1**" example.

22. This reviewer suggests that the following text be added at Line 1133:

"*Where appropriate*, the manufacturer should include specifications for other adventitious organisms including, but not limited to, viruses and prionic materials (e.g., bovine spongiform encephalopathy [BSE] and other transmissible spongiform encephalopathies [TSEs])."

The text needs to address the need to consider adding specifications for the aforementioned adventitious agents where such agents are known to be or may be present.

23. The text in Lines 1149 through 1150 states:

"Designation of certain tests such as for description, identification, assay, or impurities as PQITs would not be considered appropriate."

The preceding text should be changed to read:

"Designation of certain *evaluations* such as *those* for description, *identity*, identification, assay, *purity,* impurities, *and critical physical properties (e.g., particle-size distribution, density, and flow)* as PQITs would not be considered appropriate."

Since "description" is not a test in the scientific sense but a subjective assessment, the appropriate term is "evaluations" rather than "tests." Moreover, given the criticality of the CGMP evaluations for identity, purity, and the drug substance's key physical properties, the most commonly critical of such should be included in the list of those for which a PQIT is inappropriate.

24. The text in Lines 1205 through 1208 states:

"If the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient.[21]

[21] The current revision of an analytical procedure in a compendial monograph or general chapter should be used. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *USP* should be cited rather than *USP 25*."

The preceding text should be changed to read:

"*Unless the manufacturer developed, initially validated, and submitted the analytical procedure as the basis for* the current revision of an official compendium or other FDA-recognized standard reference (e.g., AOAC International's Book of Methods) and the referenced analytical procedure is not modified, *the submitter should submit the detailed written procedure that it uses for the analytical evaluations that it performs. When the submitter is the method's source*, a specific citation to the analytical procedure is sufficient.[21]

[21] The current revision of an analytical procedure in a compendial monograph or general chapter should be used. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *USP* should be cited rather than *USP 25*."

> Since the procedures in the official compendia and other FDA-recognized standard reference sources lack sufficient detail to ensure that those who follow their written text perform the test in a scientifically sound and reproducible manner, each manufacturer other than one who developed the test procedure should submit the detailed, written procedure and the initial validations studies that prove that the method meets its specified limits for accuracy and precision. As a Ph.D. Analytical Chemist trained in the development of analytical methods, this reviewer can assure the Agency that doing less is neither *scientifically sound* nor *appropriate*.
>
> Moreover, most of the problems found during method transfer or in the implementation of the procedures outlined in the compendia or other FDA-recognized sources arises from the lack of sufficient specificity and/or clarity in the instructional outlines provided. Common instructions like "shake" or "stir" are simple examples of the gross inexactness – the lack of specificity to: a) apparatus to be used (e.g., wrist shaker or table shaker, or, for stirrers, magnetic stirrer, ultrasonic stirrer, or blade stirrer); b) amplitude or intensity of the shaking or stirring; and c), in many cases, a minimum time or unequivocal endpoint – of the instructions provided in most published procedures. Given the preceding, it should be obvious that most manufacturers should submit the exact written procedures they use and the supporting documentation that establishes their validity.

25. The text in Lines 1280 through 1284 states:

"Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay and impurities (e.g., degradation products, residual solvents) and should be considered for other tests such as water content."

The preceding text should be changed to read:

"Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data *may* not *be* warranted for all tests. However, *specification supporting batch-representative* collated data *(at a minimum, the means, standard deviations and number of measurements)* should be provided for *each batch that addresses all the drug substance's critical variable characteristics (*assay, *purity, water content, pH, melting range, density, flow, particle distribution* and impurities *[*e.g., degradation products, residual solvents*]) that may adversely impact the uniformity or stability of the drug substance itself or the drug products made from it* and should be considered for other tests such as *the drug substance's trace-metals profile (including, as appropriate, arsenic, cadmium, calcium, lead, magnesium, mercury, potassium, and sodium) that serve to establish the manufacturing site's fingerprint for that drug substance*."

The collated information submitted should be sufficient to support the scientific validity of the specification ranges or limits established using the appropriate statistically sound techniques to extrapolate from the batch-representative data measured for a small set of batches to the most probable population limits. [**Note:** Initially, the manufacturer should set the specifications limits using a confidence level of not less than 95 % and a population coverage of 99 %. After the production history increases from the few batches in the submission to those produced over a justified period of time that covers not less than 100 batches, the specifications should be revised to use confidence level of not less than 99 % and a population coverage of not less than 99.9994%.] All variables that *may* adversely affect the stability of the drug substance and/or the uniformity of any drug product produced from the drug substance should be collated and the collation submitted. [**Note:** When the data values clearly belong to a Gaussian (normal) distribution, the minimum data reported for each critical variable should consist of the mean, standard deviation, and number of determinations made for each batch. When the data values do not clearly belong to a Gaussian distribution, the minimum data reported for each critical variable should consist of the mean, all of the individual results used to compute the mean, and the number of results.]

26. The text in Lines 1288 through 1304 states:

"E. Justification of Specification (S.4.5)

Justification for the proposed drug substance specifications should be provided. The justification should be based on relevant development data (S.2.6), information on impurities (S.3.2), standards in an official compendium, batch analyses data (S.4.1), stability studies (S.7), toxicology data, and any other relevant data. The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. When justifying the specification, an applicant should consider data from (1) drug substance batches used in evaluating clinical efficacy and safety, bioavailability, and/or bioequivalence, (2) primary stability batches, and (3) relevant development and process validation batches, when available. If multiple drug substance manufacturing sites or processes are planned, it can be valuable to consider data from these sites and processes in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance at any particular site or by any particular method. Justification for an in-process test that is used in lieu of a drug substance test should be included in S.2.4."

The preceding text should be changed to read:

"E. Justification of Specification (S.4.5)

Justification for the proposed drug substance specifications should be provided. The justification should be based on *the use of suitable* ***scientifically sound*** *and* ***appropriate statistical analyses*** *on the* relevant development data (S.2.6), information on impurities (S.3.2), batch analyses data (S.4.1), stability studies (S.7), toxicology data, and any other relevant data *using* the standards in an official compendium *for the drug substance, where such exist, or, when the drug substance is not listed in an official compendium, those for a similar drug as the basis for deriving appropriate batch acceptance criteria for batch release that include statistical quality control criteria where such are appropriate.* The discussion in this section should unify data and

information that are located in other sections of the application, either by reference or in summary. When justifying the specification, an applicant should consider data from (1) drug substance batches used in evaluating clinical efficacy and safety, bioavailability, and/or bioequivalence, (2) primary stability batches, and (3) relevant development and process validation batches, when available. If multiple drug substance manufacturing sites or processes are planned, it can be valuable to consider data from these sites and processes in establishing the *evaluations* and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance at any particular site or by any particular method. Justification for an in-process *evaluation* that is used in lieu of a drug substance *evaluation* should be included in S.2.4."

The discussion here should explicitly address the use of statistics in setting appropriate specification acceptance criteria for each batch that, where such are appropriate, include minimal statistical quality control criteria. Again, the term "*evaluation*" should be used instead of "test" especially in light of the Agency's push to incorporate PAT analyzers that classify materials based on their complex material signatures rather than measuring individual variable responses.

27. The text in Lines 1306 through 1333 states:

"• **Tests**

Inclusion of a test in the drug substance specification need not be justified. However, exclusion of a test that is normally performed on a type of drug substance, one that is recommended in a relevant FDA guidance, or one that was reported in the batch analyses (S.4.4) should be justified. Justification for the designation of a test as a periodic quality indicator test also should be provided (see section VI.A).

Occasionally, it may appear that a test performed and reported as part of the batch analyses may not be necessary or that a drug substance characteristic may not be critical to the quality of the specific drug products in which the drug substance is used. For example, the available test results for heavy metals may be very low or below the limit of detection of the analytical procedure for the batches produced in support of the application indicating that there may be no need to perform the test. However, it is not certain if the same type of results will continue to be observed for production batches because (1) limited data are available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria.[22] The proposal should include the (1) reason why the sunset provision is being proposed; (2) number of consecutive production batches that will be tested before inclusion of the test in the drug substance specification is reevaluated; (3) criteria that would be achieved, including data analysis plan, for the test to be dropped; and (4) postapproval reporting mechanism for notifying FDA of the test results when the criteria have been achieved. A *sunset test protocol* could also be considered when FDA requests that a test be added to the specification."

[22] A proposal to drop a test, based on historical data, can also be submitted postapproval in a prior approval supplement.

The preceding text should be changed to read:

"• ***Evaluation Procedures (Test, Examination, and Classification Procedures)***

In general, the firms' specifications should include all evaluation procedures required to characterize the critical chemical and physical properties that define a drug substance that is adequately uniform for the purpose or purposes for which it has been manufactured. Inclusion of *an evaluation procedure along with its sound acceptance criteria* in the drug substance specification need not be justified. However, exclusion of *an evaluation procedure* that is*: a)* normally performed on *similar* drug substances, *b)* recommended in a relevant FDA guidance, or *c)* reported in the batch analyses (S.4.4) *must* be justified. Moreover, exclusion of any procedure that is critical to the characterization of the drug substance (e.g., a specific identity test) cannot be justified. Justification for the designation of *an evaluation procedure* as a periodic quality indicator test *(PQIT)* also should be provided (see section VI.A).

Occasionally, it may appear that *an evaluation* performed and reported as part of the batch analyses may not be necessary or that a drug substance characteristic may not be critical to the quality of the specific drug products in which the drug substance is used. For example, the available results for heavy metals may be very low or below the limit of detection of the analytical procedure for the batches produced in support of the application indicating that there may be no need to perform the test. However, it is not certain if the same type of results will continue to be observed for production batches because*: a)* limited data are available at the time the application is submitted and/or *b)* the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. In these or similar circumstances, an applicant could propose a *sunset protocol* for *an evaluation*, which would provide for the *evaluation* to be dropped from the specification after an agreed number of production batches have met certain criteria[22] *provided it is kept as a PQIT with an explicit provision to reintroduce the evaluation procedure into the specification in the event that the PQIT results indicate that the change in the observed levels found become significant.* The proposal should include: *a) the* reason why the sunset provision is being proposed; *b)* number of consecutive production batches that will be tested before inclusion of the test in the drug substance specification is reevaluated; *c)* criteria that would be achieved, including data analysis plan, for the *evaluation procedure* to be dropped; and *d)* the postapproval reporting mechanism for notifying FDA of the *evaluation* results when the criteria have been achieved. A *sunset protocol* could also be considered when FDA requests that *evaluation procedure* be added to the specification. "

[22] A proposal to drop *an evaluation procedure*, based on historical data, can also be submitted postapproval in a prior approval supplement.

This reviewer again recommends using the term "*evaluation procedure*" instead of the Draft's use of the term "test." The rationale is that strictly the use of the term "test" should be reserved for procedures where the quantitative or semi-quantitative assessment of some variable factor is being conducted. In contrast, the term "evaluation procedure" obviously addresses not only test procedures but also procedures that simply examine materials or classify materials based on some complex signature without explicitly assessing the value of one or more variable characteristics that define the material.

The initial text addition was made to frame the CGMP minimums for a *scientifically sound* and *appropriate* specification. The remaining changes have been made to improve the accuracy of what is being said and to reflect the handling of a sunset provision in a manner that ensures that the evaluation procedure excluded from the specification will continue to be conducted periodically to guard against a significant future change in the level of the variable monitored by the test that is being removed from the firm's formal specification.

28. The text in Lines 1335 through 1377 states:

"• **Acceptance Criteria**

Justification should be provided for all proposed acceptance criteria included in the drug substance specification. Results from nonclinical (pharmacology and/or toxicology), clinical, and stability studies and manufacturing and analytical capability should be considered when proposing acceptance criteria. Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability. The justification should discuss the basis of the proposed acceptance criteria from the perspectives of available data and analytical and manufacturing capability and variability. Furthermore, any statistical approaches that are used to establish the acceptance criteria should be described.

Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific test because there is some uncertainty whether the same type of results will continue to be observed for subsequent drug substance batches. This uncertainty often occurs when (1) there are limited data available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. The proposal should include the (1) reason why the interim acceptance criteria are being proposed, (2) number of consecutive batches from each process (if alternative processes are used) that will be tested and/or the time frame before the acceptance criteria will be finalized, (3) data analysis plan, and (4) proposed reporting mechanisms for finalizing the acceptance criteria when the proposed final acceptance criteria are tighter, broader, or the same as the interim acceptance criteria. An applicant should not propose using interim acceptance criteria as a substitute for providing recommended or agreed upon (e.g., at pre-NDA meetings) information in an application. For example, proposing interim acceptance criteria would not be appropriate when the stability data package recommended in the ICH guidance *Q1A Stability Testing of New Drug Substances and Products* or VICH guidance *GL3 Stability Testing of New Veterinary Drug Substance and Medicinal Products* has not been provided.[23] For NDAs, finalization of interim acceptance criteria will be a phase 4 commitment.

The proposed acceptance criteria for impurities should not be greater than the levels qualified through nonclinical or clinical studies presented in the NDA. The qualified level of each impurity that is individually listed in the drug substance specification should be provided in S.3.2. Appropriate qualified levels can be obtained from published toxicology studies or guidance documents. Acceptance criteria for residual solvents should generally be based upon manufacturing capability. An applicant should consider the contribution of residual solvents in its drug product excipients when proposing acceptance criteria for residual solvents in the drug substance. See ICH *Q3C Impurities: Residual Solvents or* VICH *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*.

[23] For those applications that fall within the scope of these guidances.

The preceding text should be changed to read:

"• **Acceptance Criteria**

Justification should be provided for all proposed acceptance criteria included in the drug substance specification. Results from nonclinical (pharmacology and/or toxicology), clinical, and stability studies and manufacturing and analytical capability should be considered when proposing acceptance criteria. Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability. *In general, these allowances should be based on the use of scientifically sound and appropriate statistical procedures that properly extrapolate from the results found for the batch representative samples evaluated for each critical variable factor on a sufficient number of appropriate developmental and pre-production batches of the drug substances. In general, the minimum initial confidence level should be 95% or higher with a projected initial batch coverage of not less than 99%. In cases where an official compendium contains a drug substance monograph that establishes acceptance criteria for any post-release "in commerce" evaluation, the firm's batch release acceptance criteria must be* ***appropriately****: a) inside of any permitted range, b) below any "not more than" limit, and c) above any "not less than" limit. This is the case because the firm's inspection plans only test a small fraction (typically, less than 0.1%) of a batch and statistics has determined that, in testing small portions of a whole, the results obtained tend to be close to the batch average (in other words, if a firm wishes to determine the true limits for a factor, it must test a significant fraction of the batch [on the order of 5% to 10 % or more]).* The justification should discuss the basis of the proposed acceptance criteria from the perspectives of available data, analytical and manufacturing capability and variability, *and the statistical properties of the distribution into which the batch characteristics fall.* Furthermore, *the* statistical approaches that are used to establish the acceptance criteria should be described *and the validity of their use proven.*

Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific test because there is some uncertainty whether the same type of results will continue to be observed for subsequent drug substance batches. This uncertainty often occurs when*:* (1) *though scientifically and statistically process representative and sufficient,* there are limited data available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be *fully* characterized. The proposal should include the (1) reason why the interim acceptance criteria are being proposed, (2) number of consecutive batches from each process (if alternative processes are used) that will be *evaluated* and/or the time frame before the acceptance criteria will be finalized, (3) data analysis plan, and (4) proposed reporting mechanisms for finalizing the *batch* acceptance criteria when the proposed final acceptance criteria are tighter, broader, or the same as the interim acceptance criteria. An applicant should not propose using interim acceptance criteria as a substitute for providing recommended or agreed upon (e.g., at pre-NDA meetings) information in an application. *Similarly, an applicant should not propose using interim acceptance criteria in cases where the data collected is not statistically batch representative and/or sufficient to characterize the process at a confidence level of at least 90%.* For example, proposing interim acceptance criteria would not be appropriate when the stability data package recommended in the ICH guidance *Q1A Stability Testing of New Drug Substances and Products* or VICH guidance *GL3 Stability Testing of New Veterinary Drug Substance and Medicinal*

Products has not been provided.[23] *Similarly, a firm should not propose interim acceptance criteria based on the evaluation of a non-representative number of samples from a single batch.* For NDAs, finalization of interim acceptance criteria will be a "*P*hase 4" commitment. *Similarly, for other submissions, finalization of interim acceptance criteria will be contingent upon a written post-submission-acceptance commitment by the submitter.*

The proposed acceptance criteria for impurities should be *less than or equal to the maximum* levels qualified through nonclinical or clinical studies presented in the NDA. The qualified level of each impurity that is individually listed in the drug substance specification should be provided in S.3.2. *In many cases, the a*ppropriate qualified levels can be obtained from published toxicology studies or guidance documents. Acceptance criteria for residual solvents should generally be based upon "*best practical"* processing capability. *In cases where the applicant is also producing the drug product, the* applicant should consider the contribution of residual solvents in its drug product excipients when proposing acceptance criteria for residual solvents in the drug substance. See ICH *Q3C Impurities: Residual Solvents or* VICH *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*."

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[23] For those applications that fall within the scope of these guidances.

Again the guidance needs to explicitly assert that appropriate statistical procedures and, where post-release acceptance specifications exist in an official compendium, the in-commerce acceptance criteria for any properly stored sample must be appropriately used in establishing the release acceptance criteria for each batch. To do this, the firm must test batch representative samples from a sufficient number of batches for each chemical and physical variable factor that is critical to the characterization of the firm's drug substance. In addition, the term "*evaluation*" should be used in place of the Draft's term "test" for the reasons that have been repeatedly stated in prior comments by this reviewer.

29. The text in Lines 1429 through 1434 states:

"The types of studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include for example (1) a summary of stability batches tested, storage conditions used, attributes tested, shelf-life acceptance criteria, test schedule, amount of data available, and analysis of data (including a summary of the statistical analysis if performed) and (2) conclusions regarding the label storage conditions and retest or expiration dating period, as appropriate."

The preceding text should be changed to read:

"The types of studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include, for example*:* (1) a summary of *and the data from the* stability batches *evaluated, (2) the* storage conditions used*, (3) the* attributes *and variables evaluated, (4)* shelf-life acceptance criteria *and their justification, (5) evaluation* schedule, and *(6)* analysis of data (including *the degradation model used, the justification for the model used, and all information provided by* the statistical analysis performed) *as well as (7) the* conclusions regarding the label storage conditions and *reevaluation* or expiration dating period, as appropriate."

As has been justified previously, the term "*evaluated*" should be used in place of the Draft's "tested." In addition, this reviewer recommends that all of the information should be submitted – not just the summaries thereof. This is the case because the Agency cannot establish the validity of the summary information without having the data upon which it is based. In more than one case, this reviewer has seen the subtle but deliberate distortion of the data in the summaries provided to the Agency. The most egregious was the knowing submission of a defective test for residual solvents by one firm seeking generic approval. Almost as bad was the deliberate grouping of powder fill data by an innovator firm's statisticians in a manner that hid the fact that the true filling distribution was bimodal and presented it as a normal distribution – allowing the innovator to file for and obtain a lower fill weight target than the data supported. Based on this reviewer's experience, few, if any, of today's firms are ethical enough to be trusted to submit only summary information.

30. The text in Lines 1442 through 1447 states:

"Results of stability studies, including statistical analysis if performed, should be presented in an appropriate format (e.g. tabular, graphical, narrative). An applicant should propose a retest or expiration dating period and appropriate label storage conditions for the drug substance. There should be a direct link between the proposed, retest or expiration dating period and proposed label storage conditions and the demonstrated stability characteristics of the drug substance."

The preceding text should be changed to read:

"Results of stability studies, including *the* statistical analysis performed, should be presented in an appropriate format (e.g. tabular, graphical, narrative). An applicant should propose a *reevaluation* or expiration dating period and appropriate label storage conditions for the drug substance. There should be a direct link between*: a)* the proposed *reevaluation* or expiration dating period and *the* proposed label storage conditions*,* and *b)* the demonstrated stability characteristics of the drug substance."

For the same reasons as previously stated, this reviewer recommends using the term "*reevaluation*" in place of the Draft's term "retest." In addition, the state of today's CGMP in industry requires the submitter to have performed a scientifically sound and appropriate statistical analysis of the data supporting the proposed storage condition as well as for the accelerated studies, if any, performed. [**Note:** In general, a linear decay model for the degradation observed can be justified provided the allowed level of degradation in the drug substances over the proposed dating period is less than 10 %.] Finally, the structure of the last sentence was revised to make clear what items were being linked.

31. The text in Lines 1459 through 1463 states:

"• The analytical procedure, validation of analytical procedures and justification of acceptance criteria, as appropriate, should be included if the analytical procedure listed in the stability protocol is different from the analytical procedure described in S.4 for the corresponding test (i.e., batch release versus stability analytical procedure), or if a test included in the stability protocol is not described in S.4."

The preceding text should be changed to read:

"• The analytical procedure, validation of analytical procedures and justification of acceptance criteria, as appropriate, should be included if the analytical procedure listed in the stability protocol is different from the analytical procedure described in S.4 for the corresponding *evaluation procedure* (i.e., batch release versus stability analytical procedure), or if *an evaluation* included in the stability protocol is not described in S.4."

This reviewer again recommends using the terms "*evaluation procedure*" and "*evaluation*" instead of the Draft's "test." As stated repeatedly, these substitutions encompass procedures in which there is no testing of the samples including the case where samples are examined or classified.

32. The text in Lines 1478 through 1480 states:

"Data, other than those from primary stability studies, that support the analytical procedures, the proposed retest date or shelf life, and label storage statements can be provided.

The preceding text should be changed to read:

"Data, other than those from primary stability studies, that support the analytical procedures, the proposed *reevaluation* date or shelf life, and label storage statements *should* be provided."

This reviewer again recommends using the term "*revaluation*" instead of the Draft's "retest." As stated repeatedly, this substitution encompasses procedures in which there is no testing of the samples including the PAT case where samples are classified.

33. The text in Lines 1490 through 1491 states:

"Any results from drug substance stress testing should be provided in this section of the application."

The preceding text should be changed to read:

"Any results from drug substance stress *evaluations* should be provided in this section of the application.

This reviewer recommends using the term "*evaluations*" instead of the Draft's "testing." As stated repeatedly, this substitution encompasses procedures in which there is no testing of the samples including the PAT case where samples are classified.

34. The text in Lines 1565 through 1567 states:

"For synthetic or semisynthetic drug substances, reduced testing of materials or drug substance and/or validation of removal and/or inactivation of adventitious agents can be appropriate in certain instances, with justification."

The preceding text should be changed to read:

"For synthetic or semisynthetic drug substances, reduced *evaluation* of materials or drug substance and/or *proof* of removal and/or inactivation of adventitious agents can be appropriate in certain instances, with justification."

> This reviewer recommends using the term "*evaluation*" instead of the Draft's "testing." As stated repeatedly, this substitution encompasses procedures in which there is no testing of the samples including the PAT case where samples are classified.
>
> The term "*proof*" is more appropriate than the Draft's less exact term "validation." Since, as used in CGMP, the term "validation" encompasses an ongoing activity and what is meant here is a destination and not an ongoing activity, "proof" is the term that should be used here.

35. The text in Lines 1595 through 1597 states:

"Viral evaluation studies should demonstrate that the materials used in production are considered safe and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable."

To improve the precision and clarity of the statement being made, the preceding text should be changed to read:

"Viral evaluation studies should demonstrate that the materials used in production are considered safe and that the approaches used to evaluate *the test results obtained* and eliminate the potential risks during manufacturing are suitable."

36. The text in Lines 1635 through 1642 states:

"A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of postapproval manufacturing changes on the identity, quality, purity, and potency of the drug substance as these factors may relate to the safety and effectiveness of the drug product. Comparability protocols are optional. If a comparability protocol is proposed, it should be included in this section (R.2.S). Approval of a comparability protocol can justify a reduced reporting category for the particular postapproval change described in the protocol."

The preceding text should be changed to read:

"A comparability protocol is a protocol describing the specific *evaluations* and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of postapproval manufacturing changes on the identity, quality, purity, and potency of the drug substance as these factors may relate to the safety and effectiveness of the drug product. Comparability

protocols are optional. If a comparability protocol is proposed, it should be included in this section (R.2.S). Approval of a comparability protocol *may* justify a reduced reporting category for the particular postapproval change described in the protocol."

> This reviewer recommends using the term "*evaluations*" instead of the Draft's "tests." As stated repeatedly, this substitution encompasses procedures in which there is no testing of the samples including the PAT case where samples are classified.
>
> The use of the verb "*may*" instead of the Draft's verb "can" is more appropriate because its use conveys the reality that this option is within the Agency's discretionary purview.

37. The text in Lines 1644 through 1651 states:

"C. Methods Validation Package (R.3.S)

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. Part of the methods validation process can include FDA laboratory analysis to demonstrate that an analytical procedure is reproducible by laboratory testing. A methods validation package (multiple copies for paper applications) must be submitted in the application (21 CFR 314.50(e)(2) and 314.94(a)(10)) and should be included in this section (R.3.S)."

The preceding text should be changed to read:

"**C. 'Methods Validation' Package (R.3.S)**

'Methods validation,' *or, more properly, method qualification,* is the process of demonstrating that analytical procedures are suitable for their intended use. Part of the method-*qualification* process can include *using an ISO-17025-accredited laboratory's analytical results or the results obtained by any other FDA-recognized laboratory* to demonstrate *the inter-laboratory reproducibility of the* analytical procedure *being submitted.* A methods *qualification* package (multiple copies for paper applications) must be submitted in the application (21 CFR 314.50(e)(2) and 314.94(a)(10)) and should be included in this section (R.3.S)."

> Though the term "methods validation" is commonly used, scientifically, all that the typical data submissions do is qualify the methods being submitted for the uses specified in the submission. Thus, these are properly "*method qualifications*" – not "methods validation." As with any process, the validation of a method is a lifelong activity and not a destination. The sooner this is explicitly recognized the sooner the industry can get on with the journey – tracking the data that continually establish the validity of each qualified method for its established uses – something that few such labs seem to do.
>
> Likewise, comparative testing between laboratories is recognized as "inter-laboratory" testing. In general, the manufacturer's first choice should be to use an IS0-17025-accredited laboratory because their findings have international legal standing that other types of laboratories do not. This

reviewer's experience with FDA laboratories has been less than satisfactory in several instances including ones in which the FDA laboratory knowingly used an unqualified analytical procedure that was other than the recognized USP method to test "market basket" samples and then, *contrary to the Federal, Food, Drug, and Cosmetic Act*, attempted to take regulatory actions based on their findings. In all but one case, tests using the qualified official compendial method and the same samples failed to support the FDA lab's initial findings. This reviewer's limited experience with ISO-17025-accredited laboratories has found that, where such exist, the ISO lab used that lab's written qualified version of the official compendial method in all instances where there was a concern as to the results obtained by a non-ISO lab. [**Note:** This reviewer knows of no pharmaceutical manufacturer that has a testing and calibration laboratory that is accredited to ISO 17025 (formerly, ISO Guide 25). Moreover, most firm's testing and calibration laboratories seem to fall short of the ISO "quality" minimums in more than one key area.]

38. The text in Line 1696 states:

"• **Starting Materials with a Significant Nonpharmaceutical Market**"

The preceding text should be changed to read:

"• **Starting Materials *W*ith a Significant Nonpharmaceutical Market**"

Because the word "**with**" is the significant differentiator between this heading and the heading that follows, it should be "***W*ith**."

39. The text in Line 1708 states:

"• **Starting Materials without a Significant Nonpharmaceutical Market**"

The preceding text should be changed to read:

"• **Starting Materials *W*ithout a Significant Nonpharmaceutical Market**"

Because the word "**without**" is the significant differentiator between this heading and the prior heading, it should be "***W*ithout**."

40. The text in Lines 1740 states:

"**A. Propinquity**"

The preceding text should be changed to read:

"**A. *Relationship to the Final Intermediate***"

"**Propinquity**" is an obscure word that *means* nearness in space, time, or relationship. In the context in which it is used, it is meant to convey nearness in relationship. Moreover, from the text, the relationship is that between the starting material and the final intermediate. Since the topic is

the starting material, the obscure and cryptic "**Propinquity**" should be revised to provide a more easily understood heading such as the one proposed.

41. The text in Lines 1850 through 1853 states:

"Identification tests for a proposed starting material should be specific and should be able to discriminate between it and any related compounds that are likely to be present. More than one identification test may be appropriate. Tests to confirm the presence of a counter ion (e.g., sodium, chloride) should be included in addition to other identity tests."

The preceding text should be changed to read:

"*Identity* tests for a proposed starting material should be specific and should be able to discriminate between *the starting material* and any related *or other* compounds that *may* be present *in the starting material by virtue of the manufacturing process used or the facilities in which the starting material is produced*. More than one *identity* test may be appropriate. Tests *that* confirm the presence *and level* of a counter ion (e.g., sodium *or* chloride) should be included in addition to other identity tests. *At a minimum, one specific identity test must be included in the specification for the starting material*"

Since the CGMP speaks to identity and not identification, the tests used should be "identity tests" and not "identification tests." The preceding reality and the fact that most of the USP's "Identification" tests outside of infrared and some other spectroscopic tests are not at all material specific should lead the Agency to realize that the use of such "identification tests," while supportive of identity, are not "identity tests." Moreover, even the USP's infrared (IR) tests are not specific identity tests when they require the analyst to prepare the test samples in a manner that removes or distorts the physical properties of the material used in order to ensure that its IR spectra match those of the USP's Reference Standard. Thus, at best, most identity tests are not truly specific. Moreover, tests that only confirm the presence of a counter ion should not be used <u>unless</u> the level of the counter ion is confirmed to be appropriately close to the theoretical level for the starting material. Many substances give a positive test for ionic chloride, but few have an ionic chloride percentage close to 16.7 % by weight. Based on the preceding realities, this reviewer recommends changing the text as suggested if the Agency wants manufacturers to do identity evaluations rather that simply perform a few less than specific or non-specific "Identification" tests.

42. The text in Lines 1859 through 1863 states:

"Moreover, FDA recommends that acceptance criteria be established for all organic impurities that occur above 0.10 percent and that a limit of NMT 0.10 percent be established for unspecified organic impurities when there is greater potential for impurities originating from the starting material to carryover to the drug substance (0.20 percent for a veterinary drug substance not used in human drug products)."

The preceding text should be changed to read:

"Moreover, FDA recommends that acceptance criteria be established for all organic impurities that occur above 0.10 percent and that a limit of NMT 0.10 percent be established for unspecified organic impurities when there is greater potential for impurities originating from the starting material to carryover to the drug substance (0.20 percent for a veterinary drug substance not used in human drug products). *In cases where an impurity is highly toxic and is known to carry through into the drug substance, the appropriate level for the acceptance criteria for such impurities may need to be set at an appropriately lower level. For example, the appropriate level for a carcinogenic impurity in a drug used to treat a chronic condition might be NMT 10 ppm (NMT 0. 001 %) or less depending on the threshold limit value (TLV) established for the impurity in related primate species.*"

The guidance needs to explicitly address how to set appropriate specifications for highly toxic impurities. In the 1970's, the EPA had no problem with addressing the setting of appropriate specifications for highly toxic impurities in biocidal compound submissions for registration. However, to date, the Agency has repeatedly sidestepped directly this issue when it comes to pharmaceutical compounds. This reviewer knows that explicitly addressing this issue is long overdue and recommends that the Agency address this issue in this and all related guidances.

43. The text in Line 1871 states:

"*1. Starting Materials with a Significant Nonpharmaceutical Market*

The preceding text should be changed to read:

"*1. Starting Materials With a Significant Nonpharmaceutical Market*

Because the word "with" is the significant differentiator between this heading and the heading that follows, it should be "*W*ith."

44. The text in Line 1871 states:

"*2. Starting Materials without a Significant Nonpharmaceutical Market*

The preceding text should be changed to read:

"*2. Starting Materials Without a Significant Nonpharmaceutical Market*

Because the word "without" is the significant differentiator between this heading and the previous heading, it should be "*W*ithout."

45. The text in Lines 1907 states:

"a. Propinquity"

The preceding text should be changed to read:

"a. *Relationship to the Final Intermediate*"

"Propinquity" is an obscure word that *means* nearness in space, time, or relationship. In the context in which it is used, it is meant to convey nearness in relationship. Moreover, from the text, the relationship is that between the starting material and the final intermediate. Since the topic is the starting material, the obscure and cryptic "Propinquity" should be revised to provide a more easily understood heading such as the one proposed.

46. The text in Lines 2148 through 2149 states:

"**Identification Threshold:** A limit above (>) which an impurity should be identified (ICH Q3A or VICH GL10)"

For completeness, the preceding text should be changed to read:

"**Identification Threshold:** A limit above (>) which an impurity should be identified (ICH Q3A or VICH GL10). *In general, the limit should be stated in terms of a weight percentage*."

47. The text in Lines 2177 through 2179 states:

"**Physical Properties:** Attributes such as physical state, melting point, boiling point, solubility, hygroscopicity, color, density, refractive index, partition coefficient, crystal shape, solid state form, and particle size distribution"

The preceding text should be changed to read:

"**Physical Properties:** *Characteristics* such as physical state, melting *range*, boiling point *at a given pressure*, solubility, hygroscopicity, color, *bulk (liquids and solids) and/or tapped (solids)* density, *flow, cohesitivity,* refractive index, optical rotation, optical rotary dispersion, viscosity, partition coefficient, crystal shape, solid state form, and particle size distribution**.**"

Strictly, the term "Attributes" should be restricted to non-variable factors. Since the physical properties of a material include properties that are variable, the appropriate term should be "*Characteristics*" because it encompasses both attributes and variables. The definition provided is less exact than it should be in some instances and leaves out several key physical properties that are important in the use of the drug substance in formulating it into the drug product.

48. The following definition needs to be inserted after line 2202:

"***Purity:*** *The degree of absence of anything that is other than the defined moiety. In general, the "as is" weight-percent purity is the most useful measure of purity for pharmaceutical solid and semi-solid materials and the "as is" volume- or weight- percent purity is needed for liquid materials.*"

Though the term "purity" is often used in guidance documents and in the CGMP regulations, it is not defined. Hopefully, the definition proposed here will adequately address this oversight.

49. The text in Lines 2228 through 2232 states:

"**Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents and other components including container closure system and in-process materials. A specification sheet includes the list of tests, reference to analytical procedures, and acceptance criteria."

The preceding text should be changed to read:

"**Specification:** The quality standard (i.e., *evaluations [tests, examinations, and classifications]*, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents and other components including container closure system and in-process materials. A specification sheet includes the list of *evaluations*, reference to analytical procedures, and acceptance criteria *for a given material or material mixture*."

> Again, the term "*evaluations*" should be used instead of "tests" especially in light of the Agency's push to incorporate PAT analyzers that classify materials based on their complex material signatures rather than measuring individual variable responses.

50. The text in Lines 2251 through 2253 states:

"**Validation**: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria (ICH Q7A)

The preceding text should be changed to read:

"**Validation**: A documented program that provides a high degree of assurance that a specific process, method, or system *does* consistently *produce* a result meeting predetermined acceptance criteria (ICH Q7A)**.**"

> Since validation is a lifelong journey and not a destination, the definition must be set in the present tense. Moreover, this reviewer would suggest including a validation lifecycle that consists of a self-consistent set of qualifications spanning that lifetime. In that respect this reviewer would propose the self-consistent set:
> - **D**esign/Development **Q**ualification (**DQ**),
> - **B**uild **Q**ualification (**BQ**) *[less consistently, Installation Qualification {IQ}]*,
> - **O**peration **Q**ualification (**OQ**),
> - **E**valuation **Q**ualification (**EQ**) *[less consistently, Performance Qualification {PQ}]*,
> - **M**aintenance **Q**ualification (**MQ**), and
> - **C**losure **Q**ualification (**CQ**).